43. An insect-resistant plant comprising the plant cell of claim 16, 26, 27, 28, 29 or 30, and the insect-resistant progeny of such plant.

44. A method for controlling insects harmful to plants comprising allowing insects to ingest the plant tissue of claim 42.

45. A method for controlling insects harmful to plants comprising allowing insects to ingest the plant of claim 43.

46. The plant cell of claim 16 or 26 to which cell resistance to an insect from the group Lepidoptera, Coleoptera, Diptera, Hymenoptera, Mallophaga, and Trichoptera is conferred.

REMARKS

Attorneys for Applicants take this opportunity to thank Examiner Chereskin for allowing them the opportunity to speak with her and for the courtesy extended to them in the interview of October 31, 1991. Applicants in this amendment provide arguments and evidentiary support affirming the discovery by Applicants of a pioneering invention which derives the benefit of priority from the earliest filed application and is entitled to claims of broad scope.

Applicants have amended claim 15 to particularly point out and distinctly claim the subject matter of the invention. Insect resistance and/or the ability to control insects is particularly described in the specification at page 35, line 5; page 37, line 2; page 38, lines 14-17; page 39, line 6 through page 40, line 7; page 47, lines 5 through 20; page 61, lines 8-21; and in §12.9 at pages 121-125. Applicants note that the definition of insecticidal protein provided in the pending specification at page 47, *i*.e. "a protein or peptide that is directly or indirectly toxic or growth inhibitory under any circumstances to any insect" is in accordance with the dictionary

definition. Webster's Third New International Dictionary (copyright 1981) defines insecticidal as "destroying or controlling insects."

Applicants have added new Claims 26 to 46 which correspond to particular embodiments of the subject matter of the application that is unquestionably patentable as discussed with the Examiner during the interview. Newly added Claims 26 to 46 are, in their broadest scope, directed to a transgenic plant cell, tissue or plant to which the gene encoding a Bt insecticidal protein or active fragment under control of a functional promoter has been added and is expressed in amounts which are toxic to an insect.

Additional independent claims and claims dependent on the newly added and pending claims particularly point out and distinctly claim specific subject matter which Applicants regard as their invention which includes dicotyledonous and monocotyledonous plant cells, cells containing *kurstaki* crystal protein or fragments thereof, the *kurstaki* HD-1 or HD-73 embodiment thereof, specific types of plant cells, a method for controlling specific types of insects, full-length and truncated crystal protein embodiments, regenerated plant tissue, regenerated plants and methods for controlling insects using such plant cells, tissues or plants expressing an insecticidal protein. The newly added claims are supported in the pending specification at pages 20 to 196 and in the three figures. Particular support for different aspects of the claimed invention are discussed herein in detail at sections 1-7 of the "Claim To Priority" found below in §I below.

I. THE INVENTION AND ITS CLAIMS TO PRIORITY UNDER 35 U.S.C. §120

The Invention

By September 26, 1983, well in advance of any other scientists in the world, inventors Michael Adang and John Kemp had conceived and reduced to practice genetically modified plant cells and plants expressing an insecticidal Bacillus thuringiensis (hereinafter "Bt") protein or protein fragment under the control of a plant expressible promoter such that insect pest resistance was conferred to the plant cell, tissue or plant (as taught in specification Serial No. 535,354 beginning at page 20).[1/] In various embodiments and examples, the inventors described how to stably insert a gene coding for an insecticidal protein from Bt bacteria into the genome of a plant cell and described how to test its expression in plant tissues of a normal plant (page 54). Following ingestion of the genetically modified plant cells by insects, the insects are poisoned and thereby controlled (page 56, and see Serial No. 07/713,624 page 96 and pages 121-125 for more detailed results).

This novel feat, by no means minor, required numerous scientific steps which are detailed in the specification and

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1/ Unless noted to the contrary, all pagination refers to the first filed specification, Serial No. 535,354. Applicants recognize the difficulty encountered by the Examiner in view of the different type faces and resulting change in page numbers between the first filed application Serial No. 535,354, filed September 26, 1983; the second, CIP application Serial No. 848,733 filed April 4, 1986; the third application, which was also a CIP, Serial No. 07/260,574, filed October 20, 1988, the page numbering of which is identical to the pending FWC application Serial No. 07/713,624, filed June 10, 1991.

A table is attached hereto as Appendix A which correlates the page numbers of the first specification with the pending specification since a different type face was used to produce the CIP applications. This type face alteration resulted in a change of pagination but essentially no change was made in the disclosure other than the amplification of the invention by the disclosure of additional working examples which were appended to the end of the first specification.

include 1) the genetic manipulations needed to produce appropriate vectors and constructs that allow stable recombination into plant cells and expression of the Bt insecticidal gene from a promoter in the plant cells; 2) methods for transformation; 3) regeneration of the plant cells to produce plants; and 4) the tests needed to characterize the plants so produced.

The invention of Drs. Adang and Kemp, reduced to practice in the disclosure of Serial No. 535,354 and further exemplified in different embodiments in Serial Nos. 848,733 and 07/260,574, is broadly operable as indicated by the color photographs attached as exhibits to the Declaration of Dr. Guy A. Cardineau, filed concurrently with this amendment. The color photographs portray numerous healthy, stably transformed insecticidal plants which are startling when compared with the ravaged and decimated non-insecticidal control plants.

Worth far more than any attempt at description by words in this amendment, the visual evidence of the sickly insect survivors present on healthy insecticidal plants as compared to healthy insects found on the chewed up skeletons of non-insecticidal plants in the photograph of Exhibit 2, attests to the value, utility and significance of the invention. The foresight of the inventors, Dr. Michael Adang and Dr. John Kemp, in conceiving and then reducing this invention to practice well before any other scientists in the world, can not be minimized. One need only look to the date of publication of the art cited by the Examiner in the outstanding Office Action of 07/260,575 to recognize that the inventors reduced their invention to practice <u>years</u> before published reports of similar results by others. This pioneering invention thus performed a function not found in any earlier invention in a scientific area devoid of prior art.

The Claim To Priority

Applicants respectfully bring to the Examiner's attention the requirements needed to establish priority under 35 U.S.C. §120. These requirements are 1) that the applications have co-pendency; 2) have continuity of inventorship; 3) have specific reference to each prior application; and 4) have a disclosure in compliance with the first paragraph of 35 U.S.C. §112.

Applicants claim priority under 35 U.S.C. §120 to the first application filed September 26, 1983. The applications fulfill the co-pendency requirement because each application was filed during pendency of its parent. The applications fulfill the inventorship requirement because Drs. Adang and Kemp are the named inventors of all four applications in the chain. The applications contain or were amended to contain a reference to the earlier filed applications. Compliance with the first paragraph of 35 U.S.C. §112 is discussed below where support for the claims is identified in the specification as first filed. Additional reasons for compliance with 35 U.S.C. §112 are provided in the responses to the specific rejections of the claims.

The claims are directed to a genetically altered plant cell, tissue or plant expressing a structural gene encoding a insecticidal Bt crystal protein. The claimed cell is capable of regeneration into plant tissue and plants. The relevant disclosures related to aspects of the pending claims are noted below for specific pages of the first filed specification.

1) Plant cells, plant tissue and plants which can be made insect-resistant

The types of plants included in the disclosure of the first application as encompassed by the invention are any plant species (see, e.g. p. 22) including dicots (p. 20; p. 21, cotton or tobacco; p. 22, gymnosperms, sunflower, tobacco, soybeans,

legumes, cotton, most vegetables; p. 76, a variety of plants protectable by the invention) and monocots (p. 33; p. 76, plants protectable against insects include alfalfa, field corn, forage crops, hay, pasture plants, stored corn, stored grains, sweet corn and turf). The definition of plant cells and plant tissue on p. 27-28 includes plant cells in plants, in culture and those derived from plants. The CIP applications further exemplify different plant cells, tissues and plants used in the invention. The cells of the invention include those within plants, those derived from plants and differentiated or undifferentiated cells. The plant tissues of the invention include various plant tissues such as those from normal tissues like leaves and roots, as well as those of galls, embryos, calluses, or tissues grown in cell culture. Plants of the invention include those comprising a plant cell having a gene encoding a crystal protein or protein fragment under the control of a promoter functional in such plant cells, in which the plants are produced by any method of propagation.

2) Genetic alterations

The invention is directed to plant cells and plants, the genetic make-up of which has been altered by the insertion of heterologous DNA through any means known in the art (p. 21). The constructs are introduced into plant cells by both physical and biological methods. The examples of the disclosures describe in great detail the various constructs having different promoters and different insecticidal genes. The genetic methods used to stably recombine the promoter and Bt insecticidal gene of the constructs into plant cells are also described in detail in the examples. Large portions of the first specification are devoted to descriptions of the Agrobacterium method which was the preferred embodiment at the time of the filing of the first application, although alternative embodiments are described in

the first application. The alternative means described are directed to both physical and biological methods and include different methods of transformation (p. 8-10), DNA uptake (p. 10), the use of viral genome vectors, minichromosomes, transposons, and the use of homologous or nonhomologous recombination (p. 33). Alternate forms of delivery include the direct uptake of nucleic acid, liposome fusion, microinjection, and encapsidation (p. 33).

3) A Bt insecticidal structural gene

The application notes on p. 2 and 3 that crystal protein genes can be found on plasmids and on chromosomes of Bt, indicating where one of skill in the art could obtain relevant DNA samples. The specifications describe the use of a truncated, full-length, dicistronic or fusion construct of different Bt insecticidal structural genes. What is meant by a Bt insecticidal gene is defined on page 26 and 27. The invention recognizes that different proteins and varieties of Bt can be used (see p. 27 for related proteins) in addition to the sequenced Bt gene of *kurstaki* HD-73 found in Figure 1 and Example 1. A large number of useful varieties of Bt are found in Table 3 (at p. 77).

Information related to insecticidal proteins is provided in the background section of the specification and describes the methods known in the art for isolating, identifying and sequencing insecticidal proteins if a Bt insecticidal protein is desired that differs from those provided by example. The methods known in the art include directed or random cloning with a test of cloned fragments accomplished by feeding the bacteria containing the cloned fragment to insects with a subsequent bioassay to detect survival and/or weakening of the insect. Several Bt insecticidal genes had been cloned and identified prior to the filing of the first application (see p. 2-4 of the

specification). Additional examples provided in the CIP applications illustrate the use of Bt tenebrionis and the 5.3 class gene of HD-1.

4) A plant expressible promoter

The specification particularly describes and teaches expression in plant cells of an insecticidal structural gene under the control of a plant expressible promoter (p. 2 and defined at p. 24-25 and p. 29-30). The promoters exemplified specifically in the disclosure include the promoters of T-DNA (the 1.6, ocs, nos, tms, tml, tmr promoters at p. 25; the 35S and 19S transcript promoters of cauliflower mosaic virus at p. 26; the phaseolin promoter, p. 31 and p. 48-50; the 1.6 promoter, p. 40; and the nos promoter, p. 44-45). Other promoters described as additional examples in the CIP applications include the ORF 24 promoter.

5) Expression

Expression, an art recognized term, is defined in the specification at pp. 25, 28-30 and at other locations throughout the specification. Expression in *E.coli* was demonstrated in the first application in Example 1 and included an analysis of the protein including its functional activity against insects allowed to ingest the transformed bacteria. Expression in plant cells, tissues or plants is particularly described in the first application on page 47, page 51, and pages 54-56.

6) Regeneration

Regeneration of plants and plant tissue is described in the specification at p. 10-11 (for Agrobacterium systems using Ri or Ti plasmids); p. 21 (methods well known in the art), p. 28 (regeneration into whole plants may include steps for selecting and detecting transformed plant cells and transferring the introduced gene into commercially acceptable cultivars), p. 32 (screening methods include assays for opine production,

hybridization, immunological assays, bioassays), p. 34-35 (various aspects of regeneration known in the art and subsequent transfer into commercial cultivars), p. 47 and 51 (mating the *E.coli* strain containing the construct of the invention with A. tumefaciens, which harbors TIP plasmids containing mutations which facilitate regeneration; homologous recombinants selected; characterization by restriction mapping; testing using wounded sunflower stems; assay by ELISA, Western blots and bioassay; infection and regeneration of tobacco cells; development of breeding stock), p. 51-52 (regeneration of carrot tumors using Ri based TIP plasmids), and p. 52-54 (regeneration of tobacco and use of assays for screening the retention of the transformed phenotype).

The CIP applications further amplify and exemplify the invention disclosed in the first application with additional constructs that have different promoter/insecticidal gene combinations for producing additional insecticidal cells, tissues and/or plants for tobacco, corn, tomato, potato and cotton. As disclosed in the declaration of Dr. Guy A. Cardineau attached hereto, actual photographs and/or data are presented of the constructs of the invention as applied to the development of insecticidal gene expression in tobacco, tomato, cotton, potato, sunflower, and maize plant cells, tissues and/or plants, including different generations of plants. Moreover, the invention results in the production of healthy, uniformly transformed non-chimeric plants possessing stable germ-line incorporation of the insecticidal gene sequence. This allows transfer of the insecticidal gene sequence to subsequent generations by normal methods of sexual reproduction, as directly tested in various plants. The levels of expressed Bt protein and the stable incorporation of the Bt gene into the plant DNA have been analyzed by the various methods taught in the specification

including ELISA, Northern, Western and Southern blotting, and nucleic acid analysis.

7) Insecticidal amounts

The presence of insecticidal amounts of Bt protein in the plant cells, tissues or plants is analyzed by bioassay (see, e.g. specification §2.4 at p. 43, §3.6 at p. 47, §4.06 at 51, and Example 8 at p. 56). Alternatively, the insecticidal protein is itself detected or the nucleic acid encoding it is detected (see Example 7 at pp. 54-56 and Example 10 at p. 57). The characteristics of known insecticidal proteins are described at p. 1-4.

In further examples found in the additional disclosures of the CIP applications and as found in the declaration of Dr. Guy A. Cardineau, it is recognized that bioassays using insect feeding are the most sensitive method of assay for detection of the Bt insecticidal protein (see, e.g. the results of specific plant feeding experiments in Example 12 and §15.6 and §15.8 of the pending application). Moreover, worm weights of surviving larvae in bioassays were significantly lower than controls, and larvae that did not die failed to grow at normal growth rates. These types of bioassays, demonstrating the utility of the methods of the invention for controlling insects, are specifically depicted in the photographic exhibits attached to the declaration of Dr. Guy A. Cardineau, filed with this amendment. Significantly, the disclosures of the applications indicate that multiple generations or plants have been tested by bioassay and other methods. A careful analysis has been accomplished over a period of years to establish the stability of the inserted Bt genes and their insecticidal activity in cells of the different generations of selected plants. Such analyses are described not only in the pending specification at pages 193, but also in the declaration of Dr. Guy A. Cardineau.

II. THE INVENTION IS ENABLED UNDER 35 U.S.C. §112

In the parent Serial No. 07/260,574 application, the Examiner has rejected Claims 15-25 under 35 U.S.C. §112. Because all pending claims of Application Serial No. 07/713,624, including those added in this amendment, relate to the subject matter of Claims 15-25, Attorneys for Applicants assume that all pending claims are also rejected for the same reasons provided by the Examiner for Claims 15-25.

Attorneys for Applicants will briefly summarize the relevant legal standards under 35 U.S.C. §112, especially as they apply to pioneering inventions and will then address the specific rejections.

A. The Relevant Legal Standards

In *In re Robins*, 166 U.S.P.Q. 552 (C.C.P.A. 1970), the Court of Customs and Patent Appeals, the predecessor court to the United States Court of Appeals of the Federal Circuit, addressed the sufficiency of the disclosure of a specification to support claims of a broad scope. The Court recognized that representative examples are not required by statute nor are they the only way a broad enabling disclosure might be met. *Id.* at 555. This opinion of Judge Rich also indicated that 35 U.S.C. §112 "does not require that a specification convince persons skilled in the art that the assertions therein are correct." *Id.* at 556.

In re Goffe, 191 U.S.P.Q. 429, 431 (C.C.P.A. 1976), reversed the finding of the Board of Patent Appeals and Interferences on the issue of limitation of the claims of an application to specific materials disclosed in the examples, particularly where no prior art was relied on. In finding that the Board erred, the court opined:

> For all practical purposes, the board would limit appellant to claims involving the specific materials disclosed in the examples

> so that a competitor seeking to avoid infringing the claims would merely have to follow the disclosure in the subsequently-issued patent to find a substitute. However, to provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.
>
> *Id.* at 431.

B. The Pending Rejections Under 35 U.S.C. §112 Should Be Withdrawn

In the parent Serial No. 07/260,574 application, the Examiner rejects Claims 15-25, and thus all pending claims, under 35 U.S.C. §112, first and second paragraphs, on the grounds that Applicants have allegedly enabled only the Bt *kurstaki* sequence shown in Figure 1.

Attorneys for Applicants respectfully disagree with the Examiner's rejections under 35 U.S.C. §112 and submit that the claimed pioneering invention of Drs. Adang and Kemp is fully enabled by the earliest filed specification, allowing one of ordinary skill to make and use the invention without undue experimentation.

The Examiner is in error in her assertion that Applicants have enabled only the Bt *kurstaki* sequence of Figure 1. The first application describes multiple types of insecticidal proteins of a number of different bacterial strains. Moreover, the specification provides detailed instructions for methods of cloning, expressing, assaying and sequencing insecticidal proteins, including relevant insect bioassays. The Examiner's attention is directed to pages 24, 26-27 and page 77 of the first application.

Once such methods are taught by the specification of the first application, it is within the skill of the ordinary artisan to use the teachings of the application to substitute any insecticidal protein sequence for the Bt *kurstaki* sequence, which was exemplified only for purposes of illustration of the other detailed teachings of the specification.

A review of the references cited in the background portion of the first specification supports the position that, as of the filing date of the first application, the specification taught what was necessary to identify, clone and sequence numerous insecticidal proteins. Therefore it would be within the abilities of one of ordinary skill in the art to produce the claimed invention using the sequences of various insecticidal proteins obtained through the teachings of the specification.

Applicants note that the Hofte reference cited by the Examiner totally fails as art of any kind against <u>any</u> of the applications since it was published in 1989.[2/] The classification and nomenclature scheme iterated in Hofte in 1989 can not be used to limit an invention that is entitled to a priority date of 1983, or even of 1986 or 1988. Moreover, it is irrelevant that the Thorne reference cited by the Examiner points out the existence of multiple types of proteins with insecticidal activity because Applicants have provided instructions to one of ordinary skill in the art for cloning, isolating and sequencing a variety of insecticidal protein genes as described above. Moreover, Applicants have exemplified their disclosure using insecticidal protein sequences from Bt *kurstaki* HD-73, available as a deposited cell line, Bt tenebrionis, and a 5.3 class gene derived from Bt HD-1 dipel. This large number of examples based

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[2/] Applicants seriously question the propriety of the Examiner's citation of numerous references, published well after Applicants' filing date to bolster her §112 rejections. See *In re Hogan,* 194 U.S.P.Q. 527, 536 (C.C.P.A. 1977).

on the teachings of the first filed application should be more than sufficient to support the pending claims because they provide a variety of constructs that allow one of skill in the art to make and use the claimed invention.

Indeed, the specification of the first application makes it abundantly clear that this novel invention, not accomplished nor published by anyone else prior to the filing of the first application, encompasses the use of any insecticidal protein gene. The specification makes clear that the invention is the development of transgenic plant cells, tissues and plants containing amounts of an expressed insecticidal protein gene sufficient to affect the growth of insects susceptible to the insecticidal protein. The specification itself discloses the use of different insecticidal protein genes for different insects and provides the knowledge to those of skill in the art that healthy insecticidal cells, tissues and plants can be successfully produced.

In the parent Serial No. 07/260,574 application, the Examiner objects to the specification and rejects Claims 15-25, and thus all pending claims, under 35 U.S.C. §112, first paragraph, for failure to provide what are asserted to be proper controls, data, and table descriptions in various of the enumerated experimental insect feeding trials of the third application. Applicants respectfully submit that these criticisms impose a higher standard upon Applicants than that called for by the statute. See *In re Robins*, 166 U.S.P.Q. at page 556.

Nevertheless, in response to the Examiner's criticisms, the Examiner's attention is directed to all of the photographic exhibits attached to the Declaration of Dr. Guy A. Cardineau which supports the Applicants' disclosure of production of healthy, stably transformed insecticidal plant cells, tissues and

plants, including plants that have been produced from seed demonstrating successful germline incorporation of the insecticidal protein gene. Applicants note that normal reproductive methods can be used with plants produced according to the methods of the invention allowing the development of numerous different plant varieties.

Photographic Exhibit 2 and 3 are the visual counterparts of the specific insect trials the Examiner objects to in the Office Action. In Exhibit 3, the transgenic highly insecticidal tobacco plant leaves (designated 100) are on the left and the weakly insecticidal plant leaves (103) are on the right in the photograph. The transgenic highly insecticidal leaves of 100 are essentially untouched while all that remains of the weakly insecticidal plant leaves of 103 are larval droppings and vein stalks. Applicants disclose at p. 124 of the specification of the 260,574 application that 103 was discovered to be a non-stably transformed chimeric plant, providing an explanation that was recognized for the variable results provided in the trial description in the specification. The variability of the 103 plant however has nothing to do with the actual insecticidal nature of the healthy non-chimeric plant 100 which represents only one of the plants of the invention. The plant of clone 100 was a healthy stably transformed plant suitable for regeneration and propagation of additional plants. Moreover, providing examples of chimeric plants actually aids the person of ordinary skill in the art in making and using the claimed invention because it provides information about the number range and types of plants that need to be examined and the kind of tests needed to be done to make and use the invention.

Exhibit 8 of the declaration of Dr. Guy A. Cardineau, provides a report of a field test of transgenic insecticidal tomato plants indicating that preliminary tobacco hornworm

feeding trials were done in laboratory growth chambers to identify active plants and involved testing of 550 plants transformed with different constructs of the invention. Forty plants survived the initial testing and were used for the field trial. Although parasitization of the insects occurred in the late stages of the field trial, bioassay results of field harvested insects were consistent with the data of the other laboratory methods which showed insecticidal protein expression with toxicity of the plants in the field equivalent to that observed in the laboratory.

In summary, Applicants have used proper controls and have provided sufficient data and taught numerous methods of testing to demonstrate that the actual plant cells, tissues and plants of the invention are insecticidal. The rejection of Claims 15-25, and thus all pending claims, under 35 U.S.C. §112 first and second paragraphs have therefore been obviated. Withdrawal of the rejection of these claims under 35 U.S.C. §112, first and second paragraphs, is respectfully requested.

In the parent Serial No. 07/260,574 application, the Examiner rejects Claims 15, 16, 19 and 22-25, and thus all pending claims, directed to both dicots and monocots under 35 U.S.C. §112, first paragraph. The Examiner asserts the claims should be limited to dicots according to MPEP §706.03. Attorneys for Applicants note that the references cited by the Examiner for the proposition that success of the invention in monocots is questionable are inappropriate since the disclosures of the references are directed to the dicot species of flax (Jordan) and tobacco (Barton). This rejection is therefore improper per se because there is no evidentiary support for the Examiner's assertions that monocot transformations using foreign genes result in sick cells, tissues or plants.

In formulating this rejection, the Examiner apparently relies on a mistaken belief that working examples are required for all species of a genus described in a specification. However, working examples are not specifically required to enable an invention if the invention is disclosed in a manner allowing one of ordinary skill in that particular art to make and use the invention. Moreover, it is unnecessary to include information already known to those of skill in the art as of the filing date of the application.

The Examiner argues that the Jordan and Barton references disclose sick transformed tissue and suggests that plants containing insecticidal genes cannot be regenerated. This argument is invalid because Applicants have amply demonstrated in the disclosures of the applications and by the declaratory, photographic and written evidence of both Dr. Adang, provided previously, and Dr. Cardineau, provided with this amendment, that the invention results in healthy non-chimeric plant cells, plant tissue and plants, including those plants capable of normal sexual reproduction allowing the transfer of the insecticidal gene to other varieties of plants.

There are multiple monocot species described in the specification of the first application that the Examiner has ignored. The first application describes the invention broadly, without limitation as to the type of plant that can be developed to produce insect resistance by expression of an insecticidal gene. There is no reason that the invention does not encompass monocots, especially because the invention has been shown to include monocots as disclosed in working example 14 found at page 140-144 of the pending specification.

With regard to what was known in the art prior to the filing of the first application, the Examiner's attention is directed to the following references which are cited on PTO Form

1449 and attached as Exhibits A to C hereto: Gengenbach et al., *Proc. Natl. Acad. Sci U.S.A.* 74(11): 5113-5117 (1977); Hibberd et al., *Proc. Natl. Acad. Sci. U.S.A.* 79: 559-563 (1982); and Green et al., *Maize for Biological Research, ed. W.F. Sheridan,* p. 367-371 Plant Molecular Biology Association (1982). These references disclose monocot regeneration and gene expression and predate the original filing date of September 26, 1983. These references demonstrate the level of ordinary skill in the art at that time and show that corn plant cells and tissues are capable of regeneration into plants following transformation and stable integration of a foreign gene.

Applicants note that the Vasil reference cited by the Examiner discloses that monocot regeneration was well known in the art for various monocots well prior to the filing date of the first application, especially following the recognition that the auxin 2,4-D in nutrient medium was sufficient for induction of callus. Vasil notes plant regeneration in Gramineae in 1977 and regeneration of rice, wheat, maize and sugarcane by 1980. Vasil continues with its description of what was known in the art related to somatic embryogenesis and identification and maintenance of embryonic calli as of 1981. At page 399, Vasil states that "[S]ince [1981] efficient and long-term regeneration has been achieved in all of the important species of grasses . . . ". Attorneys for Applicants note that grasses, Gramineae, rice, wheat, maize and sugarcane are monocots. Vasil's statements regarding monocot regeneration are really directed to the efficiency of the process and not to its predictability. Vasil therefore attests to the existence of stable transformation and regeneration in monocots and supports Applicant's position that the application provides an enabling disclosure supporting the pending claims to monocot species.

In the parent Serial No. 07/260,574 application, the Examiner has rejected Claims 15-25 and thus all pending claims under 35 U.S.C. §112, first paragraph, and asserts that the claims should be limited to a full length gene Bt crystal protein, the constructs of pH 450, pH 577 or pH 578, tomato or tobacco plant cells, with toxic activity directed to M. sexta. The Examiner uses the Vaeck, Fischhoff or Barton references to suggest that expression of a bacterial gene in a plant cell is unpredictable. The Examiner also argues that toxicity against all insect species has not been demonstrated.

The Examiner is attempting to limit this pioneering invention to picture claims of certain of the exemplified embodiments based on the putative requirements of MPEP §§706.03(n) and 706.3(z). However, the use of MPEP §706.03(n) is inappropriate for this invention because Applicants have ensured that there is correspondence between the breadth of disclosure of the specifications and the drawings and the scope of the claimed invention as presently claimed. Previously pending Claims 15-25 and those newly added in this preliminary amendment are fully supported by the disclosures.

Moreover, the use of MPEP §706.03(z) is inappropriate because Applicants have disclosed numerous species, have provided a broad enabling disclosure and are therefore entitled under the law to broad claims of generic scope. In particular, Applicants have described how to clone, identify and sequence numerous Bt insecticidal genes. Applicants have exemplified four specific Bt insecticidal genes. Applicants have exemplified at least about twelve plant expressible promoters and numerous vector constructs. Applicants have specifically exemplified tobacco, carrot, sunflower, cotton, tomato, potato, and corn cells, tissues or plants produced using the methods and teachings of the invention. Applicants have demonstrated the production of stably

transformed plants that can be used for normal sexual propagation of the insecticidal gene and the development of different plant varieties. Applicants have provided laboratory data as well as field trial data and results for different plants produced according to the methods and teachings of the invention.

Applicants have produced a pioneering invention and disclosed it in the first application well in advance of any publication by another anywhere in the world. Applicants are therefore entitled to claims of broad scope. Applicants therefore respectfully request that this rejection of Claims 15-25 and all pending claims under 35 U.S.C. §112 first paragraph be withdrawn.

III. THE INVENTION IS NOT ANTICIPATED UNDER 35 U.S.C. §102

A. 35 U.S.C. §102: The Relevant Legal Standards

Anticipation is a narrow and technical attack on patentability. The standards to establish anticipation are strict. Not only must all material elements of the claimed invention must be disclosed within a single reference, the reference must comply with the novelty requirements of 35 U.S.C. §102 before an applicant loses his right to a patent. *In re Marshall,* 198 U.S.P.Q. 344, 346 (C.C.P.A. 1978). *Accord, Scripps Clinic & Research Foundation v. Genentech,* 18 U.S.P.Q.2d 1001, (Fed. Cir. 1991).

B. The Pending Rejection Should Be Withdrawn

In the parent Serial No. 07/260,574 application, the Examiner has rejected Claims 16 and 23 under 35 U.S.C. §102(b) as anticipated by Vaeck or Fischhoff, and thus rejects all pending claims related to claims 16 and 23 added by amendment herein. Vaeck was published in July 1987 and is not prior art under 35

U.S.C. §102(b) to the first or second application, and therefore is not prior art to the third application which claims priority to the first two.

Vaeck discloses the use of Agrobacterium-mediated T-DNA transfer of different chimeric Bt insecticidal protein genes of strain berliner 1715 into tobacco plants. Determinations were made of the toxicity to M. sexta larvae which were fed leaves of the tobacco plants expressing the protein.

Fischhoff was published in August 1987 and also fails as prior art under 35 U.S.C. §102(b) for the same reasons as Vaeck. Fischhoff discloses the use in transgenic tomato plants of full length and truncated forms of a B.t. *kurstaki* HD-1 insect control protein gene and reports measurements of the insecticidal toxicity of leaves of such plants for M. sexta larvae.

The Examiner has used both references as support for her assertion of anticipation based on published accounts of the toxicity of plants expressing truncated insecticidal protein genes. Attorneys for Applicants respectfully disagree with the Examiner's rejections under 35 U.S.C. §102 and submit, for reasons provided below, that the pioneering invention of Applicants is not in any way anticipated by the cited references.

Applicants bring to the Examiner's attention the teachings of the first application which describes and exemplifies a truncated gene encoding a protein that is about 90 kD at pages 37-39 of the first application. The expressed protein is proteolytically cleaved to result in an insecticidal protein fragment of about 68 kD. Moreover, the CIP applications amplify and exemplify the teachings of the specification of the first application and serve to illustrate additional truncated genes producing protein fragments that are insecticidal.

Applicants are, therefore, entitled to the filing date of the first application which predates these cited references by

several years and specifically exemplifies truncated insecticidal proteins. Toxicity of a truncated insecticidal protein gene expressed in plant cells is, thus, disclosed and exemplified in the first application. Moreover, additional regenerated plants produced according to the teachings of the first application are exemplified in the second application. Because both applications predate the cited references, this rejection and argument against the patentability of Claims 16 and 23 fails.

Applicants respectfully submit that the rejection based on the Vaeck or Fischhoff references of Claims 16 and 23, and all newly added claims that this rejection would apply to, under 35 U.S.C. §102(b) should be withdrawn.

In the parent Serial No. 07/260,574 application, the Examiner has rejected Claims 15, 16, 18 and 22-25 and thus all related pending claims under 35 U.S.C. §102(a) as anticipated by DeGreve. The Examiner is mistaken about the publication date of the DeGreve patent, probably due to the European convention of reversing the numbers for month and day as compared to U.S. convention, *i*.e. in Europe a numerical date is ordered day-month-year versus the U.S. order of month-day-year.

DeGreve was published September 3, 1986 and therefore fails as prior art under 35 U.S.C. §102 for either the first or second priority applications which do describe and exemplify expression of both truncated and full-length insecticidal proteins in plant cells and plants. Applicants have already discussed the description of a truncated insecticidal gene in the first application in the preceding paragraphs of this section. That argument will not be repeated here but additionally rebuts the Examiner's assertions as to truncated embodiments of the invention.

Applicants therefore respectfully request the withdrawal of the rejections based on the Degreve reference of

Claims 15, 16, 18, 22-25, and all the newly added claims that the rejection would apply to under 35 U.S.C. §102(a).

IV. THE INVENTION IS NOT OBVIOUS UNDER 35 U.S.C. §103

A. The Relevant Legal Standards Under 35 U.S.C. §103

As articulated by the United States Supreme Court in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966), determination of the question of obviousness requires consideration of the scope of the prior art, the level of skill in the pertinent art, and the differences between the prior art and the claimed invention. Both the suggestion to combine the teachings of the references and a reasonable likelihood of success must be found in the prior art and not in the disclosure of the Applicants. *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 529, 1531 (Fed. Cir. 1988).

B. The Pending Rejections Under 35 U.S.C. §103 Should Be Withdrawn

In the parent Serial No. 07/260,574 application, the Examiner has rejected Claims 16 and 23 and thus all related newly added claims, under 35 U.S.C. §103 as unpatentable over Vaeck or Fischhoff when taken with Wong, Held or Klier. Attorneys for Applicants respectfully disagree with the Examiner's rejections under 35 U.S.C. §103 and submit, for reasons provided below, that the pioneering invention of Applicants is not in any way rendered obvious by the cited references.

The primary references of Vaeck or Fischhoff were published in 1987, well after the filing dates of the first and second applications. The secondary references can not be used alone because they fail to predict, disclose or suggest the use of insecticidal gene constructs in plant cells. Absent the success of Applicants' invention, there is no suggestion to combine these references nor any indication that the references

could be successfully combined. A rejection under 35 U.S.C. §103 cannot be based on hindsight using the Applicants' own success as the reason for combining the references. Therefore, the Examiner's rejection is erroneous as a matter of law because the Examiner has misapplied the test for obviousness under 35 U.S.C. §103.

Applicants have already discussed in this amendment the filing date to which Applicant is entitled. Applicants have also already discussed in this amendment the Examiner's mistaken belief that truncated constructs were described only in the third application. Because truncated constructs are described in the first application and because Applicants are entitled to the filing date of the first application, neither of the primary references of Vaeck or Fischhoff are prior art to the first or second priority applications.

For the reasons provided above, Applicants respectfully request that this rejection under 35 U.S.C. §103 of Claims 16 and 23, and to all related newly added claims, based primarily on Vaeck or Fischhoff in view of the Wong, Held or Klier secondary references be withdrawn.

In the parent Serial No. 07/260,574 application, the Examiner has rejected Claims 15-25 and thus, all pending claims, under 35 U.S.C. §103 as unpatentable over the primary DeGreve reference taken with Wong, Held, or Klier. As noted above, the Examiner is incorrect about the DeGreve publication date, which is after the first or second priority date of this application. Moreover, the filing date to which the Applicants are entitled is discussed above. This rejection is, therefore, erroneous on its face since the DeGreve reference cannot be considered as prior art. The secondary references, either alone or in combination, fail to predict, suggest or disclose the development of plant cells, tissues or plants that express a Bt insecticidal gene in

amounts sufficient to affect the growth or viability of insects. Therefore, Applicants respectfully request that the rejection of Claims 15-25, and all newly added claims to which the rejection would apply, under 35 U.S.C. §103 based on the primary DeGreve reference in view of the secondary Wong, Held or Klier references be withdrawn.

In the parent Serial No. 07/260,574 application, the Examiner has rejected Claims 15-21 and 23-25, and thus all related pending claims, under 35 U.S.C. §103 as being unpatentable over Bevan, Fraley, Herrera-Estrella or Barton taken with Wong, Held, or Klier in view of Brinster.

The Brinster reference refers to mammalian constructs, eukaryotic mammalian vectors, and expression in mammalian cells and is irrelevant to plants. Bevan, published in July 1983, reports the construction of a chimeric gene encoding antibiotic resistance and its transformation into tobacco plant cells with resulting antibiotic resistance expression in the tobacco cells. Fraley is an August 1983 publication demonstrating the expression of a different antibiotic resistance gene after transformation into petunia, sunflower, carrot and tobacco cells. Herrera is a May 1983 reference disclosing the expression of a different foreign antibiotic resistance gene in tobacco cells. The Barton reference was published after September 1987 and can not be used as a prior art reference since it postdates the filing of the first and second priority applications. In sum, none of these references has anything to do with conferring insect resistance on a plant cell. Moreover, none of these references disclose antibiotic-resistant, much less insect-resistant, whole plants or specific plant tissues. Thus, based on these cited references, the Examiner has produced an improper combination of references that fails to suggest, predict or describe the claimed invention

and also fails to render the claimed invention obvious under the patent law principles related to 35 U.S.C. §103.

V. MISCELLANEOUS MATTERS

One minor point unrelated to the rejections that Applicants bring to the Examiner's attention is the correction of the filing receipt for the pending application, Serial No. 07/713,624, which has several errors in dates and the characterization of the latest application as a CIP rather than its proper designation as an FWC continuation application. The proper dates are provided in the introductory paragraph and in footnote 1 of this amendment.

CONCLUSION

The Applicants request entry of the foregoing amendments and remarks, the declaration of Dr. Guy A. Cardineau with its attached exhibits, and Exhibit references A-C with the corresponding attached PTO Form 1449 into the file of the above-captioned application. In light of the above amendment and remarks, the declaration of Dr. Guy A. Cardineau submitted herewith, previous arguments and the declaratory evidence of Dr. Adang submitted previously, Attorneys for Applicants submit that the objections to the specification and the rejections under 35 U.S.C. §§112, 102, 103 have been obviated. Withdrawal of the rejections and reconsideration of all of the pending claims is respectfully requested.

Attorneys for Applicants further submit that the claims as amended and as added herein are in form for issuance and an early allowance is earnestly requested. Attorneys for Applicants will be happy to speak with the Examiner regarding this invention and the pending claims, in the interest of rapidly prosecuting and obtaining allowance of all of the pending claims. The

Applicants would also be very appreciative if the Examiner would indicate the reasons allowance has been granted according to MPEP §1302.03. If any discussion is desired or clarification of any issue can be provided by the Attorneys for Applicants, however minor, the Examiner is respectfully requested to call Dr. Jennifer Gordon at (212) 790-9090.

Respectfully submitted,

Date: April 13, 1992

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